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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/466,698	06/06/1995	PHILIPPE SANSONETTI	2356.0043-02	3343

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EXAMINER
NAVARRO, ALBERT MARK

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 02/07/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
08/466,698	Sansonetti et al
Examiner	**Art Unit**
Mark Navarro	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *October 9, 2001 and November 9, 2001* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *24-30, 32-41, and 43-87* is/are pending in the application.

4a) Of the above, claim(s) *38* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *24-30, 32-37, 39-41, and 43-87* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☒ Certified copies of the priority documents have been received in Application No. *08/118,100* .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Applicant's amendment filed October 9, 2001 and Supplemental amendment filed November 9, 2001 have been received and entered. Claims 31 and 42 have been canceled, and new claims 47-87 have been added. Consequently claims 24-30, 32-41, and 43-87 are pending in the instant application, of which claim 38 has been withdrawn as being drawn to a non-elected invention in Paper Number 47 (received January 25, 2001).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. The rejection of claims 24-30, 32-37, 39-41, and 43-46 under 35 U.S.C. 103(a) as being unpatentable over Makino *et al* in view of Mills *et al*, Sekizaki *et al*, Naddif *et al* and Ozenberger *et al* is maintained. Additionally this rejection is applied to newly added claims 47-87.

Applicant's are asserting that the instant claims do not read on any method of inactivating a gene by allelic exchange or deletion mutagenesis, rather the claims read on a specific method, where a gene is inactivated "other than only by inactivation by means of a transposon inserted into the gene." Applicant's further assert that each of Mills *et al*, Sekizaki *et al*, and Ozenberger

et al, the mutant is first created by insertion of a transposon, and then subsequently involved in homologous recombination or allelic exchange. Applicant's further assert that Ozenberger *et al* is used to generate deletion mutations in vitro, in particular the enterobactin region is placed into a recombinant plasmid and various deletion mutants are generated using restriction endonuclease and ligase enzymes. Applicant's further assert that since Ozenberger *et al* generated minicells, and that minicells were not known to be produced in Shigella, one of ordinary skill in the art would not be motivated to preform deletion mutagenesis on strains of Shigella. Applicant's finally assert that since the only way that the cited references disclose for inserting a selection marker is by inserting a transposon, there is no indication of how one of ordinary skill can use the deletion mutagenesis technique of Ozenberger to rectify the deficiencies of Mills, Sekizaki and Ozenberger. Applicant's arguments have been fully considered but are not found to be fully persuasive.

Applicant's arguments are not found to be persuasive in view of the combined teachings of Makino *et al,* Mills *et al*, Sekizaki *et al*, Naddif *et al* and Ozenberger *et al.*

First, Applicant's are asserting that the instant claims do not read on any method of inactivating a gene by allelic exchange or deletion mutagenesis, rather the claims read on a specific method, where a gene is inactivated "other than only by inactivation by means of a transposon inserted into the gene." However, allelic exchange and deletion mutagenesis are both means of inactivating a gene "other than by means of a transposon." Even assuming that a transposon was originally used to inactivate the gene, subjecting the mutated gene to undergo

allelic exchange results in the transfer of the mutation to a new strain which then becomes mutated by means other than "only by inactivation by means of a transposon inserted into a gene."

Second, Applicant's further assert that each of Mills *et al*, Sekizaki *et al*, and Ozenberger *et al*, the mutant is first created by insertion of a transposon, and then subsequently involved in homologous recombination or allelic exchange. However, this results in bacterial strains having a mutated gene which were not directly transformed with the transposon. The transposon was passed on via recombination, thus the strain was mutagenized by means other than only a transposon being transformed into the strain in vitro.

Applicant's further assert that since Ozenberger *et al* generated minicells, and that minicells were not known to be produced in Shigella, one of ordinary skill in the art would not be motivated to preform deletion mutagenesis on strains of Shigella. However, It has long been held that a reference must be evaluated in its entirety, not on the basis of its preferred embodiments or working examples. In re Mills, 470 F.2d 649, 651, 176 USPQ 198 (CCPA 1972). Ozenberger *et al* did generate minicells, however the technique of generating deletion mutagenesis is not limited solely to cells which generate minicells. Ozenberger *et al* further report that "protein expression in minicells (data not shown) indicated that deletion of the internal 1.3 kb EcoRV fragment resulted in the loss of only P7 (one protein). (See page 3643). Clearly this minicell retained sufficient DNA to express proteins other than that of P7, which was specifically deleted as a result of the mutagenesis.

Applicant's finally assert that since the only way that the cited references disclose for inserting a selection marker is by inserting a transposon, there is no indication of how one of ordinary skill can use the deletion mutagenesis technique of Ozenberger to rectify the deficiencies of Mills, Sekizaki and Ozenberger. However, as set forth in the previous response Makino *et al* teach of generating transposon insertions into the icsA gene. Those of ordinary skill in the art recognize that transposons, which insert themselves into a given recognition sequence are also very capable of removing themselves from that site, and thereby allowing for the previously mutated gene to revert to normal function. This point has been addressed by the teachings of Mills *et al.* (See last paragraph). It is this precise teaching that one of skill in the art would be further motivated to incorporate a further method of mutagenesis, such as deletion mutagenesis as taught by Ozenberger *et al*, to prevent a reversion to virulence.

Makino *et al* (Cell Vol. 46, pp 551-555, August 1986) teach of a region on the large virulence plasmid of Shigella (virG gene/icsA gene) is required for cell-cell spread and is involved in the pathogenesis of Shigella. Makino *et al* further teaches of transposon insertions into this region, and that the mutant may be a plausible candidate for a vaccine. (See page 554 and abstract).

Makino *et al* does not teach of inactivating the virG/icsA gene by means other then a transposon.

Mills *et al* (Vaccine Vol. 6, pp 116-122, 1988) teach the attenuation of Shigella can be achieved by loss of, or deletion of genes from the large virulence plasmid that specifies bacterial invasion as well as site directed inactivation of the toxin gene. Mills *et al* teaches the potential for reversion to virulence represent possible problems. (See last paragraph).

Sekizaki *et al* (Infection and Immunity Vol. 55(9) pp 2208-2214, 1987) teach of methods of replacing the Shigella toxin gene with a mutant allele. Sekizaki *et al* suggests that toxin production is hazardous.

Ozenberger *et al* (J. Bacteriology Vol. 169 pp 3638-3646, 1987) teaches of using methods of insertion and deletions of the siderophore gene enterobactin to impair the ability to grow.

Nassif *et al* (Infection and Immunity Vol. 55 pp 1963-1969, 1987) teaches of a Shigella flexerni mutant which no longer produces the siderophore aerobactin displays altered extracellular growth capacity. Nassif *et al* teaches that it would not be expected to provide sufficient attenuation, but it would certainly be considered additional security. (See last paragraph).

Given that Makino *et al* have generated Shigella strains with inactivated icsA genes via transposon insertions and that these strains have vaccine potential, and that transposon mutants have the potential for reversion to virulence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have attenuated Shigella by inactivating genes required for bacterial invasion or Shigella toxin as described by Makino *et al* and Sekizaki *et al*, and inactivation of the gene required for aerobactin as taught by Nassif *et al* using methods

of allelic exchange and deletion mutagenesis as taught by Mills, Sekizaki *et al*, and Ozenberger *et al* for the expected benefit of developing a vaccine since as described by Sekizaki *et al* toxin production is a hazard in a vaccine.

For reasons of record in Paper Number 45 as well as the reasons set forth above, this rejection is maintained.

The following new grounds of rejection are applied to the amended claims:

Claim Rejections - 35 USC § 112

2. Claims 58-73 and 82-87 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims recite "so that said modified strain of Shigella does not comprise an active icsA gene" as well as not comprising an active aerobactin or enterochelin gene.

Applicant's have not specifically pointed to support for this precise limitation. While Applicant's have clearly mutated these genes throughout the specification, the limitation that the strain "does not comprise an active icsA gene" is deemed new matter. For instance, if the strain contained two or more copies of the gene, the strain could have the icsA gene mutated while the

second copy of the icsA gene was active. Applicant's are required to demonstrate clear support for the newly claimed limitation (page and line number) or cancel the newly added material.

3. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Navarro, whose telephone number is (703) 306-3225. The examiner can be reached on Monday - Thursday from 8:00 AM - 6:00 PM. The examiner can be reached on alternate Fridays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Lynette Smith can be reached at (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 1645 by facsimile transmission. Papers should by faxed to Group 1645 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the official Gazette 1096 OG 30 (November 15, 1989). The CMI Fax Center number is (703) 308-4242.

Mark Navarro

Primary Examiner

February 6, 2002